REMARKS

As a preliminary matter, Applicant thanks Examiners Steele and Schultz for their time and courtesy during the telephonic interview on September 27, 2007. Claim amendments were discussed and no final conclusions were reached. The amendments and remarks herein reflect the discussion during the interview.

Claims 1, 3, 5-7 and 9 - 21 are currently pending in the application. No claims are presently withdrawn from consideration. Claims 2, 8, and 16 are cancelled. Claims 1, 3, 5, 7, 9, 10, 17, 19, and 21 are amended. Support for the amendments can be found throughout the claims and specification as discussed below. Claims 22-26 have been added. The newly added claims are supported throughout the specification. Specifically claims 22-24 are supported on page 15 in Example 2; claim 25 is supported on pages 19 and 20 in examples 5 and 6; and claim 26 is supported on page 5. The Examiner has rejoined claims 10 and 12 in view of the amendments to claim 1. No new matter has been added.

Status of the Claims- Rejoinder

Applicant thanks the Examiner for rejoining claims 10 and 12 in the instant application. Applicant has changed the status identifiers to indicate this status change.

Withdrawal of Objections

Applicant thanks the Examiner for the withdrawal of the objections to claims 2, 8, and 11-12.

Rejection of Claims 1, 3, 5-7 and 9 - 21 Under 35 U.S.C. §112, first paragraph

Written Description

Claims 1, 3, 5-7 and 9 - 21 are rejected under 35 U.S.C §112, first paragraph as failing to comply with the written description requirement. Applicant respectfully traverses the rejection.

The Office Action states that the invention as claimed encompasses all known fusion proteins and all potential fusion proteins since virtually any protein can be cleaved. Further, the Office Action states that the claims encompass cleavage of the cleavage site impairs infection.

The Office Action also states that the structural limitation that the protease is specific for the cleavage site and not for any other location in the polypeptide is not present in the claimed invention, but that these elements are taught by the specification.

Without agreeing with the rejection and purely to progress the prosecution of the application, Applicant has now included the limitations of the cleavable site being a *sequence specific protease* cleavable site, providing a definite structure; and that the sequence specific protease cleavable site within the displayed polypeptide is protected by folding of the polypeptide or otherwise either absent from the virus, or inaccessible to cleavage, or present only in bacteriophage proteins not required after bacteriophage assembly to mediate infection. These amendments are supported, for example on page 4, lines 19-26, and page 6, lines 20-22 and provide structural information as required by the Examiner.

Applicant submits that one skilled in the art would understand that the inventors were in possession of the structure of a "sequence specific protease cleavable site" at the time of filing. Indeed, the application also describes such sites (e.g. page 9, lines 5-13). It is well within the ability of those skilled in the art to identify protease cleavable sites in addition to those provided in the specification.

Further, as is fully described in the present response applicant submits that one skilled in the art would understand where and how to insert a protease cleavable site into a displayed polypeptide based on the teachings of the instant application.

Bacteriophage are resistant to proteases. This is discussed in the instant specification (see page 10, lines 9-12, see also US Patent 5,780,279, col. 8, ln 43-45, cited in the specification). This provides the opportunity to insert specific cleavage sites into surface proteins required for infection, "for example at junctions between domains" as noted. The relative sensitivity or insensitivity of folded and unfolded proteins to proteases is discussed in the specification, for example on page 10, lines 16-19. It is noted that protease sensitive site is "flexible, accessible, and capable of local unfolding." Moreover, methods for selection of protease specific sequences is well known in the art (see, e.g., Example XV of US Patent 5,780,279). Therefore, methods to identify and select protease cleavage sites is provided in the specification.

As the Office Action notes, the test for sufficiency of support under the written description requirement was provided by the Court in *Vas-Cath, Inc. v. Mahurkar*, 935 f.2d

1555, 19 USPQ2d 1111 (Fed. Cir. 1991), which stated, "Although [the applicant] does not have to describe exactly the subject matter claimed... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (citations omitted). It is not required that the Applicant be in possession of every possible embodiment of the invention at the time of filing. Applicant is not required to be in possession of every known and unknown heterologous polypeptide, every known and unknown bacteriophage coat protein, every known and unknown fusion protein, every known and unknown bacteriophage, and every known and unknown protease cleavage site as suggested in the Office Action.

Applicant respectfully submits that the written description requirement does not necessitate an encyclopedic recounting of all known or yet to be discovered sequence specific proteases and their corresponding protease cleavage sites, or other components of the claims, that might be claimed or used in the method of the invention when a generic description is provided. To hold Applicant's claimed method to this sort of standard is inappropriate and deprives Applicant of protection for the full scope of the claimed invention. Further, Applicant has not just provided a generic description, but has provided sequence specific proteases, their cleavage sites, and a sequence including multiple cleavage sites for practicing the method of the invention. The Examiner further notes that the specification provides two examples of properly folded polypeptides that make cleavage sites inaccessible and allow for bacteriophage propagation.

Applicants directs the Examiner to the teachings of the Examples in the instant specification and to their demonstration of the method of the invention. Applicant provides a brief overview of the teachings of the Examples and strongly encourages the Examiner to contact Applicant if further clarification is required. It is noted that prophetic examples can be used to meet the requirement for written description.

Example 1 demonstrates the resistance of phage to proteases and conditions that can be used to make the phage sensitive to protease. These data suggest that infectivity of phage will not arbitrarily be decreased with protease treatment. Moreover, the Examples provide conditions under which cleavage can be carried out to promote exposure of protease cleavage sites.

Example 2 provides an exemplary embodiment of a sequence to be inserted into the flexible glycine-rich region between the D2 and D3 domains of p3 phagemid.

Example 3 demonstrates that the site rationally selected in the embodiment is accessible to proteases and that protease cleavage substantially reduces bacteriophage infectivity consistent with indications that only a small fraction of the bacteriophage express a fusion protein when rescued with helper phage.

Example 4 teaches the construction of an scFv library containing antibodies for binding to a specific antigen. The generation of the library requires the use of phagemid DNA including the scFv library in conjunction with a helper phage that includes a trypsin cleavage site in gene 3 which is protected upon recombination with the phagemid. Phage libraries are selected using a myc-tag, and then treated with trypsin to cleave the helper phage that do not contain an scFv sequence. The library is substantially enriched for phage containing an insert.

Example 5 demonstrates that wild type (properly folded) and mutant (improperly folded) forms of barnase can be used to provide a proof-of-concept of the instant invention. By using proteins that have substantially similar sequences, but substantially different folding, the "proteolytic selection" method of the invention is demonstrated. "Proteolytic selection" results in a 10^4 –fold enrichment of the protease resistant version of barnase after one round of selection and 10^6 – fold enrichment after two rounds at 37°C. These data demonstrate that the methods taught in the specification can be used to differentiate between folded and unfolded proteins.

Example 6 demonstrates a similar selection as Example 5 using villin rather than barnase. A 10^3-fold enrichment of properly folded phage was found after a single round of protease selection.

Examples 5 and 6 demonstrate that multiple sequences can be used as "flexible linkages" for protease sensitive sites to practice the method of the invention, and that the sensitivity of a specific site to cleavage can be modified for example by an increase in temperature.

Example 7 demonstrates the selection of a signal sequence based on translocation of a polymerase. The selection for display of the polymerase is done by cleaving specifically the helper phage p3 copies with the protease trypsin so as to render non-infective all phage particles that are not expressing any p3-polymerase fusion protein. After three rounds of antibody based selection methods, most clones include deletions of the polymerase gene (4 of 28), and after four rounds, 28 of 30 include deletions. Using a second selection method, 3 of 12 of the clones include deletions after four rounds. In round five, the protease cleavage step of the invention is

added. After selection rounds six and seven, 3 of 13 and 0 of 19 clones represent deleted p3-polymerase fusions. These data demonstrate that the methods of the invention are useful to select against improperly folded or mutant proteins.

Example 8 demonstrates the selection of an active DNA polymerase using a proximity effects by crosslinking a reaction substrate to a bacteriophage, and selection for a chemically tagged product. Again, cleavage of the protease sensitive site in the helper bacteriophage used to construct the library substantially enrich the library for bacteriophage containing properly folded proteins. Western blots were used to demonstrate poor incorporation of the p3-polymerase fusion protein into the phage relative to the p3 protein of the helper phage, about 1 of 1000. Selection resulted in a yield of about 1-5% infectious bacteriophage. The selection substantially improved the yield of catalytically active polymerases from 0.037% to 2.4%.

Example 9 demonstrates the selection of disulphide containing peptides. The example includes the use of a short, flexible amino acid linker sequence AGGAAA to provide flexibility to the fusion protein to provide access to proteases. Bacteriophage are generated and subject to two rounds of proteolytic selection and are analyzed for binding to barstar, their specific ligand. 17 of 18 clones randomly selected and treated with a combination of trypsin and thermolysin during the selection were found to bind barstar. Similarly, 5 out of 8 and 9 out of 14 clones treated with only trypsin or thermolysin, respectively, were found to bind barstar. No randomly selected clones not treated with protease during the selection were found to bind to barstar.

Applicant submits that the multiple examples, both prophetic and performed demonstrate that Applicant was in possession of the invention at the time of filing. The methods teach the use of multiple protease sensitive sites and multiple proteases for significant enrichment of phage, typically at least 10^3, for selection of bacteriophage expressing proteins with desired characteristics.

The Office Action refers a number of cases to demonstrate the standard of disclosure necessary to meet the requirement for written description. The fact patterns of these cases are clearly distinct from the facts in the instant claims. In *Fiddes v. Baird* (citation omitted), a finding of lack of written description was made for the broad class of mammalian FGF's when only the bovine sequence was provided. Similarly, *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* and *Fiers v. Revel* (citations omitted) cited in the Office Action are also drawn to related or

variant nucleic acid and protein sequences of the single sequences disclosed when the related or variant sequences were not known at the time of the filing. The Office Action further cites *Enzo Biochem* (citations omitted) wherein the disclosure was related to the use of probes that were only a small part of the entire genomic sequence, when only the full genomic sequence was without further guidance as to what sequences could be properly used as probes. *Noelle v. Lederman* (citation omitted) is another case in which a mouse sequence was provided, and claims to a human sequence were desired.

Applicant submits that these cases are not relevant to the possession of specific protease cleavage sites for known (or even unknown) proteases as multiple sequence specific proteases and their cleavage sites were known at the time of the filing, as demonstrated by the listing of the sequence specific proteases in the specification. Moreover, the invention is not a particular sequence specific protease and its corresponding cleavage site. This is distinct from the cases cited wherein the sequence *was* the invention claimed (or desired to be claimed). Applicant submits by common use of the term "sequence specific protease cleavable site" as now claimed (referred to as a "protease recognition site for cleaving" in the pGEX expression vector information enclosed herewith as Appendix A and discussed below) that those skilled in the art would immediately recognize such a structure based on its physical properties. In the cases cited by the Examiner, one skilled in the art would not recognize a nucleotide or amino acid sequence as being the correct human nucleotide or amino acid sequence provided with a sequence from another single, non-human species. Similarly, one would not recognize specific probes within a genomic sequence provided with the full genomic sequence and no further guidance. Applicant submits that one skilled in the art would readily recognize a sequence specific protease cleavable site based on the teachings of the specification and the knowledge of those skilled in the art.

In re Curtis (citation omitted) presents a fact pattern that is opposite of the claims of the instant invention. In Curtis, a single species was disclosed that would not bring to mind multiple members of the genus. Curtis disclosed that a "microcrystalline wax adheres to expanded polytetrafluoroethylene dental floss and increases its coefficient of friction so as to create commercially acceptable product." It was determined that the disclosure of the single species did not support the genus of "friction enhancing coatings for PTFE dental floss." *In re Curtis* did

note when disclosure of a single species *would be sufficient* to demonstrate possession of a genus.

> Disclosure naming single species can support later-filed claim to genus that includes that species if person of ordinary skill in art, reading initial disclosure, would "instantly recall" additional species of later-claimed genus already "stored" in their minds, but if later-claimed genus would not "naturally occur" to person of ordinary skill upon reading prior disclosure, then unpredictability in performance of species other than that specifically enumerated defeats claim to priority based on initial disclosure.

The instant specification provides a number of sequence specific proteases. Applicant submits that a listing of proteases to one skilled in the art would prompt the person to "instantly recall" additional species. Again, the case has no bearing on the instant claims. Provided with the term "sequence specific protease cleavage site" even in the absence of the examples provided in the specification, one skilled in the art would be able to "instantly recall" any of a number of such sites and the corresponding proteases to cleave such sites. Similarly, one skilled in the art would be able to "instantly recall" that properly folded proteins are typically protease resistant and that flexible linker regions, either naturally occurring or inserted, need to be present in proteins to allow for cleavage.

The Office Action further states that the "laundry list" disclosure of potential proteases and protease cleavage sites does not meet the written description requirement as it does not lead those skilled in the art to any particular species citing *Fujikawa v. Wattanasin* (citation omitted). The case is not relevant to the instant application. In *Fujikawa v. Wattanasin*, a motion by the senior party was denied in an interference to add a sub-genus count to compounds for inhibiting cholesterol biosynthesis, since only a large genus of compounds was disclosed by the junior party. This fact set is clearly distinct from the issues in the instant case. Applicant has provided a list of sequence specific proteases of the genus of sequence specific proteases. Applicant does not wish to specifically claim a sequence specific protease not listed in the specification. Proteases other than those listed in the instant specification are known, and are known to have a specific function, to catalyze the cleavage of proteins, and can be used within the scope of the invention. Moreover, Applicant broadly claims the use of sequence specific proteases and does not wish to lead one skilled in the art to any particular protease. As demonstrated by the

specification, the protease is a matter of choice to be selected by the individual practicing the invention. The use of a specific protease is not a limitation of the instant invention.

The initial burden of proof in establishing whether the claims are supported by an adequate written description falls upon the Examiner. "The description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption" (MPEP 2161.04 and *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA1971)). Furthermore, the Examiner "must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting a preponderance of the evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims" (*In re Wertheim*, 541 F.2d at 263, 191 USPQ at 97 (CCPA 1976)). The Examiner has not provided sufficient evidence to demonstrate that one that one of skill in the art provided with the disclosure of the specification would not recognize Applicant to be in possession of protease cleavable sites, and sites for their insertion into displayed fusion polypeptides in bacteriophage coat proteins is protected by folding of the polypeptide wherein the sites are otherwise either absent from the bacteriophage, or inaccessible to cleavage, or present only in bacteriophage proteins not required after bacteriophage assembly to mediate infection as now claimed.

The claims have been amended to recite that the protease cleavable site is located within the polypeptide and, to further clarify the location, that this site within the polypeptide is protected by the folding of the polypeptide. The specification, particularly the Examples provided therein, demonstrate that proper folding of a protein results in protease resistance. Further, the Examples provide teachings of the use of different proteases and different cleavage sites demonstrating that the inventors were in possession of the invention. The claims have been amended to recite further structural and functional properties of the sequence specific protease cleavage site. Methods to design and select protease cleavage sites in expressed fusion polypeptides with these properties were in possession of the inventors at the time of filing as demonstrated by the specification.

The Office Action further states that the claims do not include any structural information regarding folding of the polypeptide that could prevent cleavage by the protease. The specification clearly demonstrates that proper folding results in protease resistance. Moreover,

the specification teaches how to test proteins and viruses for resistance to proteases. The specification also teaches methods to increase protease sensitivity without decreasing infectivity.

Applicant submits that there is adequate written description as the skilled person would readily understand from the specification that the Applicant was in possession of the full scope of the invention at the time of filing. As such, Applicant respectfully requests withdrawal of the written description rejection and allowance of the claims.

Enablement

The Examiner has rejected claims 1, 3, 5-7 and 9 - 21 under 35 U.S.C. §112, first paragraph. The Examiner asserts that while the specification is enabling for a method of selection of a virus comprising providing a virus encoding and displaying barnase mutant A or villin with a cleavage site, exposing the virus to cleaving agents and propagating the virus in a manner that makes the cleavage site inaccessible, the specification does not "enable a person skilled in the art to make and use the invention commensurate in scope with the claim." Applicant respectfully disagrees and traverses the rejection.

Applicant has amended the claims to specify that the cleaving agent is a protease that recognizes the sequence specific protease cleavable site in a bacteriophage. Further, claim 1 has been amended to recite that the cleavable site is present in the displayed polypeptide at a site that is protected by folding of the polypeptide and is otherwise either absent from the bacteriophage, or inaccessible to cleavage, or present only in viral proteins not required after bacteriophage assembly to mediate infection. One of skill in the art, given the disclosure of the instant specification, particularly with the Examples which are discussed in detail above, and the level of knowledge and skill in the art, would be able to perform the invention as claimed.

As stated in the MPEP at § 2164.01(a):

> There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:
>
> (A) The breadth of the claims;
>
> (B) The nature of the invention;
>
> (C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The Office Action provides a detailed analysis of the Wands factors in relation to the disclosure and claims of the instant specification and claims. In regards to the breadth of the claims, the Office Action states that they are unduly broad for not specifying a specific cleavage agent. The claims now recite a sequence specific protease. Applicant submits that the specific identity of the polypeptide sequences expressed adjacent to the protease cleavage site is not relevant to the activity of the protease. This is demonstrated by the availability of a number of expression vectors including protease cleavage sites for removal of fusion tags after protein expression.

Applicant encloses herein as Appendix A a copy of a plasmid map from GE Healthcare including a large number of variants of GST-fusion protein expression vectors (pGEX Vectors, GST Gene Fusion Systems). The vectors include a glutathione S-transferase sequence; one of three sequence specific protease cleavage sites, thrombin, Factor Xa, and PreScission™ Protease; and a multiple cloning site for insertion of the sequence of choice of one skilled in the art for expression. Applicant notes that the document was stated to be first published in 1993, prior to the filing date of the instant application. As the products have been sold for an extended period of time, it is expected that the product substantially functions as expected, allowing for production of a GST-fusion polypeptide and subsequent cleavage of the tag without cleavage of the expressed, presumably folded, polypeptide. These plasmids demonstrate that those skilled in the art were capable of cleaving fusion polypeptides using thrombin and FactorXa by the insertion of specific sequences between two polypeptide domains expected to properly fold. Applicant submits that it is well within the ability of those of skill in the art to insert a sequence for expression adjacent to a sequence for sequence specific protease cleavage.

The Office Action states that the level of predictability is high in the expression of fusion proteins and bacteriophage particles, but that the state of the art is low in regard to decreasing

infectivity by protease cleavage as demonstrated by Kristensen and Winter, and Sieber et al. Applicant submits that the claims are drawn to sequence specific protease cleavable site located within the displayed polypeptide and which site is protected by folding of the polypeptide and is otherwise either absent from the bacteriophage, or inaccessible to cleavage, or present only in viral proteins not required after bacteriophage assembly to mediate infection. Therefore, the sequence must be in a place that is known to be accessible and/or is accessible by design.

The Kristensen and Winter (1998) reference was specifically discussed during the interview. The Examiners noted that using proteases FactorXa, Arg-C or thrombin, the single specific sequence in the construct was not cleaved. However, the single sequence was cleaved by five other proteases. Applicant notes that the proteases tested by Kristensen and Winter were all tested against a single sequence under a single condition. Applicant submits that one skilled in the art would be able to design protease cleavage sites that can be cleaved by the protease FactorXa, Arg-C, or thrombin (e.g., by inserting the sequence present in the pGEX vectors for cleavage by thrombin or Factor Xa). Moreover, the reference demonstrates that the testing of multiple proteases for cleavage of a sequence is routine in the art, and that testing proteases for cleavage under multiple conditions is also routine in the art (see, e.g., Table 1). Applicant submits as the Kristensen and Winter paper was not directed to the characterization of proteases and their cleavage sites, and that three proteases were identified that were able to promote essentially complete loss of infectivity of the bacteriophage particles. There was no motivation to attempt to promote cleavage of the sequence with further proteases. The results in Table 1 of the reference clearly demonstrate that Kristensen and Winter likely could have modified conditions to promote cleavage by FactorXa, Arg-C, or thrombin, but that there was no reason to spend the money, time, or resources on such an endeavor.

Claim 1 does not require that the sequence specific protease cleavage site have the sequence used in the Kristensen and Winter reference. Examiners agreed that proteases and their use were well known and understood in the art. Moreover, the specification provides conditions that can increase susceptibility of proteins to cleavage by proteases (as does the Kristensen and Winter reference in Table 1). Provided with the teachings of the Kristensen and Winter reference, one skilled in the art would be taught to test multiple proteases, and conditions to promote cleavage when cleavage under native conditions does not occur. Applicant strongly

disagree with the characterization of the teachings of the Kristensen and Winter reference that the claimed methods cannot be practiced with proteases found not to cleave a single specific sequence under a single set of conditions.

The Office Action notes limitations of protease cleavage methods indicated in Kristinsen and Winter including that phage must be resistance to proteases, proteins must be exported to the phage surface, a cleavage site must be chosen for a specific protease, and the fusion protein must cleave after nicking with non-covalent attachment. In regard to the first limitation, it is well known that phages are protease resistant. This was further demonstrated in the instant specification. In regard to the second limitation, the Office Action states that the predictability of expression of fusion proteins on virus particles is high. Applicant concurs that there are no enablement issues related to this step. In regard to the third limitation, it is noted that the Examiner states that a cleavage site must be chosen for a specific protease. Applicant concurs that the protease to be used and the specific sequence to be inserted into the fusion polypeptide is a matter of choice. The possibility to use one or more proteases to cleave a specific sequence is clearly contemplated by the inventors (see, e.g. Example 9 of the specification discussed below). Sequences for use for protease specific cleavage are well characterized (including thrombin, Arg-C, and FactorXa cleavage sites) and the routine nature of selection of a specific protease is demonstrated by the long available pGEX vectors (see, Appendix A). In regard to the fourth limitation, it is clear that cleavage would occur after nicking without non-covalent attachment in at least most cases. Further, methods for treatment to reduce disulfide bridges are found in Example 9.

Regarding Sieber, Applicant submits that the reference relates to a rapid method for selection of stabilized variants of a protein and selects from a large repertoire of variants that are only marginally more stable than others. This is different to the present method of selecting virus encoding intact (folded) native fusion polypeptides from those expressing unfolded polypeptides. Hence selection from a large repertoire of variants that are only marginally more stable than others according to the method of Sieber may work better with compact monomeric proteins, but that does not suggest that the presently claimed method can only work with such proteins.

Indeed, it is stated that even the method of Sieber should be generally applicable to globular proteins so long as a large repertoire of sequences can be generated (see page 958, paragraph 5). Hence, Sieber does not teach that teach that the state of the art/unpredictability of the art is high.

The level of skill in the art is high. Therefore, one skilled in the art provided with the teachings of the specification would be able to practice the method of the invention.

The amount of direction provided by the specification and the number of working examples is high. Applicant points to the discussion of the Examples above and submits that the specification provides a substantial number of working examples.

The quantity of experimentation needed to make or use the invention is routine. Applicant submits that in the biotechnological arts, the amount of experimentation is frequently time consuming and may be difficult, but if sufficient direction is provided by the specification and success can reasonably be expected, the experimentation is routine. Applicant submits that the Examiner is not considering what is an ordinary amount of experimentation in the art of the instant application. This must be considered in the analysis of what constitutes "undue experimentation." *In re Wands* states:

> The determination of what constitutes undue experimentation in a given case requires application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* (citation omitted). The test is not merely quantitative because a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. (pg. 1404)

Applicant submits that the experimentation required to practice the methods of the invention is routine, and the specification provides substantial guidance with respect to the direction in which experimentation should proceed.

The Examiner seems to suggest that in order for the claim to be enabled, it is necessary for all constructs to be functional in the methods of the invention. Applicant respectfully

disagrees. *In re Wands* teaches that a limited level of success, so long as there is some success, is sufficient to meet the enablement requirement.

During prosecution *Wands* submitted a declaration under 37 C.F.R. §1.132 providing information about all of the hybridomas that Appellants had produced before filing the patent application. The first four fusions were unsuccessful and produced no hybridomas (i.e., failed). The next six fusion experiments all produced hybridomas.

Of all of the fusion experiments performed by *Wands*, only four of the nine fully characterized hybridomas produced antibodies that fell within the scope of the claims. The specific sequences of the hybridoma antibodies was not known prior to their identification, but based on functional characteristics, hybridoma cell lines expressing antibodies with the desired characteristics were identified using predictable (e.g., detailed and likely successful) time, money, and reagent intensive methods. *Wands* did not teach an improved method for making hybridomas. *Wands* taught and claimed a method that required the use of hybridomas having specific claimed characteristics. An additional 134 hybridoma lines were frozen and stored without further analysis. The number of these hybridomas that produce antibodies that fall within the limitations of the claims is unknown.

Wands demonstrates that routine experimentation is not always trivial or successful. Routine experimentation can include animal testing. Routine experimentation, by the nature of it being experimentation, has some aspect of uncertainty in regard to result, which is tolerable within the scope of enablement. If the experimental path and data analysis have sufficient certainty (*i.e.*, are routine), the claims are enabled. *Wands* makes it clear that not all outcomes from routine experimentation need to fall within the scope of the claims in order for the claims to be enabled.

In view of the knowledge and level of skill in the art, the specification provides specific teachings to support enablement of the claims. In *In re Angstadt* (537 F.2d, 190 USPQ 218 (CCPA 1986)) the number of species disclosed for the enablement of claims was discussed.

> Having decided that appellants are *not* required to disclose every species encompassed by their claims even in an unpredictable art such as the present record presents, each case must be determined on its own facts (emphasis in original).... Appellants have, in effect, provided those skilled in this art with a large but finite list of transition metal salts

> from which to choose in preparing such a complex catalyst. Appellants have actually carried out 40 runs using various transition metal salts and hexaalkylphosphoramides. If one skilled in this art wished to make and use a transition metal salt other than those disclosed in appellants' 40 runs, he would merely read appellants' specification for directions how to make and use the catalyst complex to oxidize the alkylaromatic hydrocarbons, and could then determine whether hydroperoxides are, in fact, formed. The process discovered by appellants is not complicated, and there is no indication that special equipment or unusual reaction conditions must be provided when practicing the invention. One skilled in this art would merely have to substitute the correct mass of a transition metal salt for the transition metal salts disclosed in appellants' 40 runs. Thus, we have no basis for concluding that persons skilled in this art, armed with the specification and its 40 working examples, would not easily be able to determine which catalyst complexes within the scope of the claims work to produce hydroperoxides and which do not.
>
> Since appellants have supplied the list of catalysts and have taught how to make and how to use them, we believe that the experimentation required to determine which catalysts will produce hydroperoxides would not be undue and certainly would not "require ingenuity beyond that to be expected of one of ordinary skill in the art." *Fields v. Conover*, 58 CCPA 1366, 1372, 443 F.2d 1386, 1390-91, 170 USPQ 276, 279 (1971).

In the instant case, Applicant has provided a large number of "runs" in considering the disclosure of the specification. In this, Applicant has provided those skilled in the art with a large but finite list of sequence specific proteases and sequence specific protease cleavage sites, and sites for insertion into the heterologously expressed polypeptide to allow for cleavage. The specification also provides cleavage assays and methods to increase proteases sensitivity such that one skilled in the art would be able to test constructs prior to insertion into bacteriophage for expression. One would be easily determine which combinations of protease and protease cleavage site would function and which would not. Data are provided regarding the sensitivity of phage to various denaturants and proteases to allow for selection of conditions to be tested to promote cleavage of the heterologously expressed peptide that will not substantially disrupt infectivity of the phage.

In re Angstadt (at 219) further cited the Supreme Court decision of *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 270-71 (1916), in discussing the adequacy of the disclosure of the froth flotation process of ore separation.

> Equally untenable is the claim that the patent is invalid for the reason that the evidence shows that when different ores are treated preliminary tests must be made to determine the amount of oil and the extent of agitation necessary in order to obtain the best results. Such variation of treatment must be within the scope of the claims, and *the certainty which the law requires in patents is not greater than is reasonable*, having regard to their subject-matter. The composition of ores varies infinitely, each one presenting its special problem, and it is obviously impossible to specify in a patent the precise treatment which would be most successful and economical in each case. The process is one for dealing with a large class of substances and the range of treatment within the terms of the claims, while leaving something to the skill of persons applying the invention, is clearly sufficiently definite to guide those skilled in the art to its successful application, as the evidence abundantly shows. This satisfies the law. *Mowry v. Whitney*, 14 Wall. 620; *Ives v. Hamilton*, 92 U.S. 426, and *Carnegie Steel Co. v. Cambria Iron Co.,* 185 U.S. 403, 436, 437. [Emphasis added by CCPA.]

Similarly, preliminary tests to select the desired sequence and protease for cleavage of the site under specific reaction conditions based on teachings of the specification (e.g., see Example 1). Variation is allowed within the scope of the claims to select different proteases, different protease cleavage sites in both sequence and location within the protein, and different heterologous proteins. The selection of the protease and cleavage site will leave something to the skill of persons in the art, but sufficient guidance is provided to guide those skilled in the art to its successful application.

Routine experimentation does not exclude repetition of methods disclosed in the specification. In a more recent decision:

> The court concluded that those "experts" to whom CellPro referred in support of its argument either were not experts, did not follow the teachings of the patent, or otherwise did not engage in undue experimentation. As to those experts that only had success in producing a suitable antibody after several attempts, the court concluded that " [r]outine repetition of a patent's specification to achieve a desired experimental result does not constitute undue experimentation." (*Johns Hopkins Univ. v. CellPro* , Civ. No. 94-105-

RRM, at 5 (D. Del. Feb. 24, 1997) (citing *PPG Indus., Inc. v. Guardian Indus. Corp.* , 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623-24 (Fed.Cir. 1996) in *The Johns Hopkins University v. Cellpro Inc.*, 47 USPQ2d 1711 (Fed. Cir. 1998))

Applicant submits that the methods for practicing claimed invention are no less predictable, and perhaps more predictable, than the generation of hybridomas as was done by Kohler and Milstein in *Hopkins v. CellPro*. Repetition to optimize experimental conditions are routine in the art.

Based on the amended claims and arguments presented above, Applicant submits that one of skill in the art would be fully enabled to perform the invention commensurate in scope with the claims. Applicant respectfully requests withdrawal of the rejection.

CONCLUSION

In view of the above amendments and remarks, Applicant believes the pending application is in condition for immediate allowance. Any additional fee occasioned by this paper may be charged, or overpayment credited to, Deposit Account 04-1105, Reference No. 208039/1090.

Respectfully submitted,

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Name: Colleen McKiernan
Registration No.: 48,570
Customer No.: 29933
Edwards Angell Palmer & Dodge LLP
P.O. Box 55874
Boston, MA 02205
Tel: 617-239-0100